

REMARKS

Upon entry of the amendments herein, claims 1-25 and 28 remain pending in the application. Claims 1, 13 and 28 have been amended herein; and claims 26 and 27 have been cancelled. No new matter has been introduced by any of the amendments herein.

I. Introduction

Applicants and the undersigned acknowledge with gratitude the time taken by Examiners Ly and Marschel to participate in an interview in Alexandria to discuss the outstanding issues and provide their input. The amendments and remarks now presented reflect, as required in the Interview Summary issued following the meeting, the substance of the interview.

II. Rejections under 35 U.S.C. §112, 1st Paragraph

Claims 13 and 14 have been rejected under 35 U.S.C. §112, 1st paragraph as failing to comply with the written description requirement based on an allegation that new matter had been introduced in Applicants' previous amendments. This issue was discussed during the interview, and it was agreed that deletion of the word "value" from claim 13 would dispose of this concern. This amendment has been made and the rejection should be withdrawn.

Claims 26 to 28 remain rejected under 35 U.S.C. §112, 1st paragraph as being nonenabled. During the interview, Professor Ned Wingreen, one of Applicants, presented to the Examiners an explanation of how one derives the values of h_1 via h_0 . Applicants maintain that there is sufficient disclosure to allow one to practice the invention described in claims 26 to 28. Nonetheless, in the interest of expediting the prosecution of this application to allowance and without acquiescing in the rejection, claims 26 and 27 have been cancelled. Claim 28 has been amended to depend from claim 1, from which 26 ultimately depended. Applicants reserve the right to resume prosecution of the cancelled claims in a continuation application.

III. Rejection under 35 U.S.C. §102(b)

Claims 1-8, 13-15, 20, 23 and 24 remain rejected under 35 U.S.C. §102(b) as being anticipated by the Science article of Dahiyat et al. In the Examiner's response to Applicants' previous arguments, the Examiner stated that the limitation argued by Applicants to distinguish the claimed invention from the disclosure of Dahiyat was not found in the claims and the arguments were therefore not persuasive. The Examiners indicated during the interview that addition of the limitation in question would be helpful but might not by itself remove all of the prior art issues. Applicants have amended the preamble

of claim 1 to incorporate the previously argued limitation. Support for the amendment can be found on page 9, lines 14-20 of the specification.

At the interview, Professor Wingreen further explained to the Examiners why the Dahiyat disclosure does not disclose all of the elements of the claimed invention.

As Professor Wingreen explained, Dahiyat fails to disclose critical elements of the claimed invention. The method disclosed in Dahiyat is specifically aimed at identifying a new sequence of amino acids that will adopt a prespecified, previously known, and naturally occurring backbone configuration. Since the method is applied only to such a prespecified backbone, Dahiyat absolutely fails to disclose the elements of the inventions as claimed, namely, a means for identification of backbone configurations that not only were previously unknown but are realizable. Dahiyat states, in partial part:

1) On page 82, second column, the first sentence in the section entitled **Sequence selection** states: "Our design methodology begins with a backbone fold and we attempt to select an amino acid sequence that will stabilize this target structure."

2) "In order to assess the capability of our design algorithm, we have computed the entire amino acid sequence for a

small protein motif. We sought a protein fold that would be small enough to be both computationally and experimentally tractable, yet large enough to form an independently folded structure in the absence of disulfide bonds or metal binding. We chose the $\beta\beta\alpha$ motif typified by the zinc finger DNA binding module." [Beginning of second paragraph, third column, page 82.]

3) In referring to the structure of FSD-1 (the optimal sequence or Full Sequence Design identified by the Dahiyat method), Dahiyat states: "The comparison of supersecondary structure parameter values and backbone coordinates highlights the excellent agreement between the experimentally determined structure of FSD-1 and the design target, and demonstrates the success of our algorithm at computing a sequence for this $\beta\beta\alpha$ motif." [Last sentence, first paragraph, second column, page 86.]

4) A particularly strong example of the fundamental difference between the Dahiyat concept and method and the claimed design method is shown in the following Dahiyat passage: "The sequence selection algorithm requires structure coordinates that define the target motif's backbone (N, C α , C, and O atoms and C α -C β vectors). The Brookhaven Protein Data Bank (PDB) (13) was examined for high-resolution structures of the $\beta\beta\alpha$ motif, and the second zinc finger module of the DNA binding protein

Zif268 was selected as our design template (9, 14)." The claimed method is not itself a sequence selection algorithm, nor does it employ such an algorithm at any point. Furthermore, the claimed method does not require (nor would such be desired) predetermination of structure coordinates to set the design process in motion.

5) Fig. 6 in the Dahiyat reference strikingly confirms that the structure obtained by the Dahiyat method is for all practical purposes the prespecified natural backbone configuration.

Dahiyat clearly fails to teach each and every element of the claimed design method; for that matter, as shown above, it must be appreciated that the primary Dahiyat reference cannot even be said to suggest the claimed invention, let alone anticipate it. This rejection should be withdrawn, and such withdrawal is respectfully requested.

IV. Rejection under 35 U.S.C. §103(a)

Claims 1-25 also remain rejected under 35 U.S.C. §103(a) as being obvious over the same Dahiyat reference in combination with U.S. Patent No. 6,403,312, also to Dahiyat et al. The clarifying amendments discussed above and the specific Dahiyat disclosure also presented above clearly show the differences between the claimed invention and the method disclosed in the

primary Dahiyat reference and further make clear the deficiencies in that reference.

Although the Examiner first invoked the Dahiyat article as an anticipatory reference, in leveling this obviousness rejection he concedes the deficiencies of the article, and contends that the Dahiyat patent as a secondary reference, discloses features that are admittedly absent from the Dahiyat article. In summary, it is the Examiner's stated belief that the primary Dahiyat reference discloses the design of "stable, well-folded proteins with a fully automated novel sequence selection," that the secondary Dahiyat reference teaches "using a protein library" and that the skilled artisan would have been motivated to combine these two teachings. However, whether or not the Examiner's assertions are true regarding what the two references supposedly teach and regarding motivation to combine those teachings, combination of the teachings would not lead one of skill in the art to the instantly claimed invention.

As made clear above in Section III, among other shortcomings Dahiyat fails a) to disclose a means for identification of previously unknown, realizable backbone configurations and b) to disclose that determination of structure coordinates is not required for effective protein design. In fact, the Dahiyat article teaches that such a determination is required; on the other hand, the use of such

predetermined parameters would unnecessarily and undesirably limit the practice of the present invention.

These disclosures are not found in the Dahiyat patent, either. Neither the alleged teaching of the secondary reference of the use of a protein library nor the specific teaching of the use of a conjugate gradient method also attributed by the Examiner to the secondary reference furnish the teaching that the Dahiyat article fails to provide. Accordingly, the Examiner has failed to meet his burden of establishing a prima facie case of obviousness. More particularly, the Examiner has failed to establish that the combination of the cited references discloses all elements of the invention as claimed, that it would reasonably lead one of ordinary skill in the art to the claimed invention or that there would be motivation to combine the teachings (and, again, such combination is insufficient anyway). This rejection should therefore be withdrawn.

V. Conclusion

The amendments to the claims have addressed the new matter and enablement issues raised by the Examiner. Furthermore, the combination of claim amendments and arguments presented above make clear the patentable distinction between the claimed invention and the teachings of the cited references.

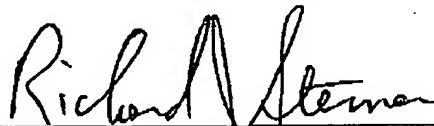
Reconsideration and allowance of the application with pending

claims 1-25 and 28 are respectfully requested. Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any additional fees which may be due for any reason in connection with this communication to Deposit Account No. 23-1703.

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Respectfully submitted,



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